Methadone

REVIEW ARTICLE

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Summary: Methadone and acetylmethadol, although possessing almost all of morphine's pharmacological properties, differ from other morphine-like drugs in their longer action, more gradual and less intense withdrawal syndrome, and blockade of euphoric effect of other opiates in addicts. A high percentage of patients maintained on methadone are better able to hold employment or to be otherwise socially productive than when dependent on heroin or morphine.

A review of published results and procedures used in methadone maintenance treatment programs for heroin dependence is presented. Former heroin addicts are usually maintained on 80 to 120 mg. (high dose) or 20 to 60 mg. (low dose) oral methadone daily. Some programs are reported to have produced 80% success (patients employed or otherwise socially productive). Selection of patients, availability of allied therapeutic and rehabilitative facilities, strict control of supply, record keeping and periodic evaluation are considered essential.

Different criteria ("drug-free" vs. "socially productive") for judging "success" of treatment of heroin-dependent persons by methadone maintenance and administrative problems in large-scale treatment programs constitute the principal aspects of controversy.

Résumé: *La méthadone: revue de son emploi*

La méthadone et l'acétylméthadol, bien que possédant presque toutes les propriétés pharmacologiques de la morphine, en diffèrent par leur action plus longue, un syndrome de sevrage plus graduel et moins intense et un blocage des effets euphoriques qu'exercent les autres opiacés chez les narcomanes. Un fort pourcentage d'héroïnomanes ou de morphinomanes traités à la méthadone parviennent mieux à garder un emploi ou à jouer un rôle actif dans la société que lorsqu'ils dépendaient des deux dérivés précités.

Le présent article passe en revue les résultats publiés et les méthodes utilisées dans les programmes de réhabilitation des héroïnomanes. Les anciens héroïnomanes peuvent être généralement "maintenus" avec des doses quotidiennes de 80 à 120 mg (dose forte) ou de 20 à 60 mg (dose faible) de méthadone per os. Certains programmes annoncent avoir obtenu 80% de succès (malades employés ou jouant un rôle actif dans la société). Le choix des malades, la disponibilité des traitements connexes et des installations de réhabilitation, le contrôle rigide du renouvellement des médicaments, l'enregistrement et l'évaluation périodique des malades sont considérés comme des facteurs essentiels.

Les principaux aspects des questions en discussion sont l'emploi des divers critères utilisés ("libérés de la drogue" et "actifs sur le plan social") pour juger du "succès" du traitement à la méthadone des anciens héroïnomanes et les problèmes administratifs que posent les programmes de réhabilitation sur une large échelle.

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The number of opiate narcotics addicts in Canada known to the Narcotic Control authorities in 1969 was a little over 4000.[1] The opiate-using population in Canada in 1972 was "conservatively estimated" by the Le Dain Commission[2] to be at least 10,000. A 1973 report[3] estimated the number of persons with drug-dependence on heroin in the United States to be 560,000. This rapid increase in prevalence of heroin dependence in recent years and intensified governmental concern and efforts towards treatment and rehabilitation of heroin addicts have at least partly contributed to the increased frequency of reports and discussions on methadone not only in the medical journals but also in the mass news media.

The number of heroin addicts under treatment in methadone maintenance programs increased from the initial 22 cases in one New York program in 1964[4] to an estimated 10,000 in some 60 programs across the United States in December 1970.[5] Another estimate gave 9000 as the number of former heroin addicts under treatment in methadone maintenance programs in the United States and Canada in early 1971.[6] By April 1972 the U.S. Food and Drug Administration estimated that some 60,000 were receiving methadone maintenance treatment in the United States.[7] The 1971 suggestion[6] for expanding the methadone maintenance case load in New York City to some 25,000 over the next three years (i.e. 1971-74) was by mid-1972 more than half fulfilled — an estimated case load of 16,000 on methadone maintenance in New York in April 1972 was reported.[8]

On the other hand, while this expansion of methadone maintenance programs for the treatment of persons with heroin-dependence has the approval and support of governments and medical associations in both the United States and Canada,[7,9-14] this modality of treatment and its attendant problems have also evoked some controversy. This may be seen in a few examples of titles and subtitles of some recent reports in scientific and medical journals which are usually not considered sensation-mongering publications. Three such examples are: "The methadone illusion",[15] "Methadone: an alternative to the 'official view'",[16] and "Drug abuse: methadone becomes the solution and the problem".[17] Some of this controversy is related to problems of administration and control, but judgement of success by different criteria by advocates and critics (e.g. "drug-free" vs. "socially productive") also gives rise to differences of views.

Both administrative problems and the criteria for judging "success" of treatment of heroin-dependent patients with methadone maintenance are at least indirectly related to the pharmacological properties of methadone itself.

Chemistry

Methadone, which is 4,4-diphenyl-6-dimethylaminoheptan-3-one (I), was synthesized in Germany during World War II as a synthetic substitute for opiate analgesics.[18] The ability of methadone to substitute for opiates (whether as analgesics or for preventing drug-hunger in opiate addicts) may be partly understood from the structural relationships between methadone and opiates and opiate-surrogates, as illustrated by the conformational structures shown in Fig. 1 — II (methadone), III (morphine) and IV (meperidine).[18,21] Such structural relationships led Beckett and Casy[19,20] to suggest that the methadone structure could fit the same stereospecific analgesic receptor as morphine. The pharmacologically active stereoisomer of methadone is its

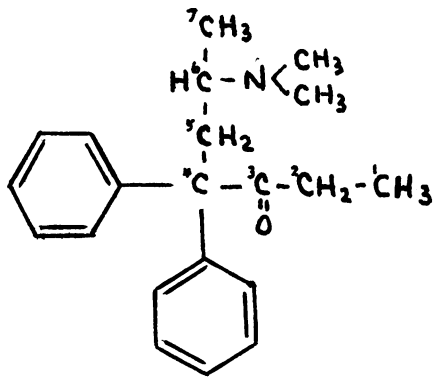
(−)-isomer (l-methadone) which has the R-configuration at its carbon-6 position (with the different chemical groups oriented around that carbon in a certain spatial order).[18,21] The dextrorotatory (+)-methadone (d-methadone) would have the orientation of the chemical groups around that carbon-6 position in an opposite fashion (referred to as S-configuration). The levorotatory (—)-methadone has approximately twice the analgesic potency of morphine,[21,23] whereas (+)-methadone is reported to be less than one tenth as effective.[18,21] The clinical implication of the metabolic conversion of the almost inactive (+)-methadone to the more active (—)-methadol will be further discussed later in connection with metabolism.

Pharmacology and use in addiction

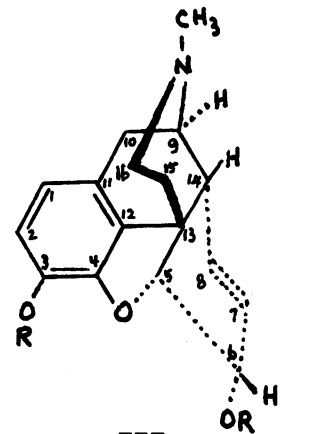
Methadone possesses almost all the pharmacological properties of morphine, including the analgesic and other depressant actions on the central nervous system, and development of tolerance and drug-dependence.[22,25] It also effects cross-tolerance and cross-dependence with other morphine-like drugs.[10,12] It suppresses the abstinence syndrome in an opiate-dependent person from whom morphine-type drugs have been withdrawn (such as in acute detoxification). But methadone differs from other morphine-like narcotics in several significant respects:

1. Methadone's action (especially with large oral doses) is much more prolonged than the other morphine-like drugs.
2. Methadone withdrawal syndrome is slower in onset (often with few or no symptoms on the first day of withdrawal), less intense, more gradual and prolonged in comparison with withdrawal from morphine or heroin.[10]
3. Oral methadone, in appropriate high-tolerance dosage schedules and "stabilized" on long-term administration, blocks, in opiate-dependent persons, the euphoric effect of subsequent doses of other morphine-like drugs, and abolishes craving ("drug hunger") of former addicts for the original drug.[4,10-12,26-28] This blockade effect does not occur if methadone is taken by opiate addicts by injection, or taken by non-addicts orally or by injection.[5] Methadone by injection produces behavioural effects in both opiate addicts and non-addicts, similar to those produced by other morphine-like drugs.[12,25] Methadone administered orally or parenterally does not block the effects of non-opiate drugs.

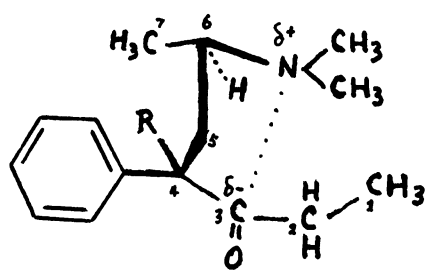
Other than as an analgesic, from the mid-1940s to mid-1960s methadone was also used in the treatment of withdrawal syndrome in the acute detoxification of patients with morphine-type dependence. In 1964 Dole and Nyswander[4] initiated the new approach in the use of methadone in the treatment and rehabilitation of persons with drug-dependence on heroin, and soon extended their program to the treatment of large numbers of criminal heroin-addicts[27] by what has now come to be known as methadone maintenance treatment. This modality of treatment involves the oral administration of methadone to the heroin-dependent person (while abstaining from all morphine-like drugs) in gradually increasing dosage (usually from an initial 10 to 20 mg. oral dose per day) over an induction period of several weeks until the patient is stabilized on a very high daily oral dose of the order of 80 to 120 mg. This magnitude of dosage is based on the original technique of Dole's programs and appears to be fairly widely used in other methadone maintenance programs.[11,12] A



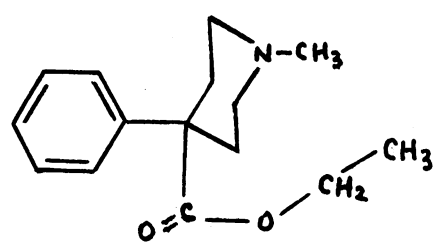
I
Methadone



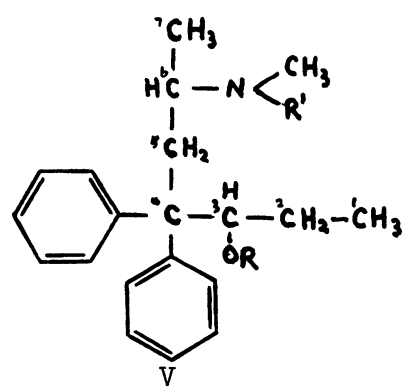
III
Morphine R = H
Heroin R = -C-CH3 (O)



II
Methadone



IV
Meperidine



V

		R	R'
(a)	Methadol	H	CH_3
(b)	N-Demethylmethadol	H	H
(c)	Acetyl Methadol	-C-CH_3 (O)	CH_3

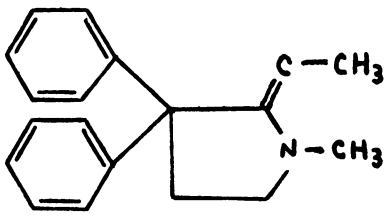
FIG. 1—Conformational structures of methadone, methadone derivatives, opiates and opiate-surrogates.

number of authors[11,29-31] have also reported successful methadone maintenance treatment by using considerably lower daily doses (20 to 60 mg.). As high a daily maintenance dose as 180 mg. has also been reported.[32] The patient may then be maintained on the "stabilized" daily dose for months or even years with concurrent psychiatric (when required) and/or social rehabilitative measures and periodic evaluations.

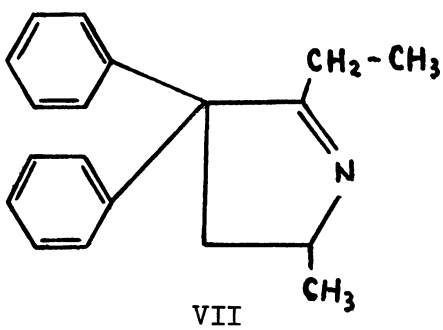
Two important effects of methadone maintenance treatment of heroin-dependent persons appear to be:

1. While maintained on methadone, a high percentage of these patients seem to be able to live a more socially productive life (holding jobs, taking care of home, etc.) than when they were dependent on heroin or other morphine-like drugs.
2. The high, stabilized daily dose of methadone blocks the euphoric effect of street doses of heroin that may be illicitly taken; this helps to eliminate the former heroin addict's desire to return to heroin.

The American Medical Association Council in its report[10] distinguishes methadone substitution treatment from maintenance treatment as follows: in the use of methadone for suppressing abstinence syndrome in the acute withdrawal of heroin from addicts (acute detoxification), if methadone administration (including both stabilization and its general withdrawal) goes beyond three weeks, it is considered to be methadone maintenance. In methadone maintenance therapy, the American Medical Association Council Report,[9,11] the Canadian Medical Association-Department of National Health and Welfare joint committee report[12] and those conducting such programs[6,29] all emphasize the necessity of selection of patients, concurrent rehabilitative measures, strict control of methadone administration and supply, prevention of diversion to illicit use, urinalysis for opiates (to ascertain whether tolerance is maintained), availability of various supportive services (psychiatric, vocational, detailed record-keeping and periodic evaluations). It is generally considered necessary that the daily administration of oral methadone in a noninjectable form (usually in fruit juice) be carried out in the presence of the physician or his appointed agent (pharmacist or nurse), and that such close observation and supervision should continue until the patient shows adherence to the program and progress towards rehabilitation. Frequently this requires a period of six months or so,[11] but would obviously vary, perhaps widely, with different patients. On the other hand, when at a later stage a patient shows sufficient progress towards rehabilitation, more than one day's supply of maintenance methadone may need to be entrusted to him.[6]



VI
"Metabolite 1"



VII
"Metabolite 2"

FIG. 2—Metabolites of methadone.

Acetylmethadol *vs.* methadone

Up to the present, methadone used for maintenance oral doses has been mostly tablets of (±)-methadone hydrochloride (usually administered in a noninjectable liquid such as fruit juice) which, at the stabilized high dosage, produces effects lasting 24 to 36 hours. Therefore, a daily dose taken at a treatment centre by the ambulatory patient would not require additional take-home doses. But the necessity for the patient to make daily visits to the treatment clinic for the methadone dose over a period of months, especially if the patient is holding a job, would be a disadvantage. There is also the problem of doses for weekends. In the past three years or so, a longer-acting derivative of methadone has been tried in maintenance treatment, namely α(—)-acetyl methadol (also known as α(—)-methadyl acetate.[33-35] Zaks, Fink and Freidman[33] reported that 80 mg. of α(—)-acetyl methadol suppressed narcotic hunger as effectively as 100 mg. of methadone hydrochloride. The effects of acetyl methadol following oral administration of a stabilized maintenance dose extend over a 48- to 72-hour period, thus making it possible to administer one maintenance dose on alternate days instead of a daily methadone hydrochloride dose.[33-35] In molecular structure, methadol is methadone with its C_3 carbonyl replaced by a secondary alcoholic function, and in acetyl methadol (methadyl acetate) the acetyl group is linked, by ester linkage, to the C_3 alcoholic hydroxyl group. The apparent steric "anomaly" is that the most active pharmacological form of acetyl methadol (and of methadol) is the α(—)-isomer which has the S-configuration at C_3 and at C_6 and it is therefore derived from the practically inactive (+)-methadone that has the 6S configuration, not from the highly active (—)-methadone which has the 6R configuration. It may be noted here that the clinically more active α(—)-acetyl methadol, when given to animals by intraventricular administration, is a much less potent analgesic than its α(+)-isomer, and it has been suggested that the analgesic (and presumably other pharmacological) effects of the (—)-isomer may be due to a metabolite rather than the intact drug itself.[36] Portoghese[37] offered another explanation by suggesting that hydrogen-bonding *donors,* at dipolar sites of analgesic receptors, may interact with the C_3 carbonyl group in (—)-methadone (6R), whereas the C_3 hydroxyl group in α(—)-methadol (3S:6S) may interact with hydrogen bonding *acceptors* at the analgesic receptors' dipolar sites.

Withdrawal from methadone

Withdrawal from methadone after long-term maintenance at high daily dosage levels of the order of 100 mg., when the need arises (e.g. when the patient asks to leave the program or is discharged for misconduct), would usually be undertaken by gradual reduction over several weeks.[27] Lipkowitz, Schwartz and Lazarus[32] have reported four cases where the abrupt withdrawal of methadone from patients who had been on such high maintenance doses produced only a mild syndrome and that severe subjective symptoms reported by the patients could not be objectively verified. Tice and Pascarelli[38] objected to this conclusion by pointing out that the four patients reported by these authors were evaluated under conditions of arrest and imprisonment, and illicit narcotic supply in prisons cannot always be excluded. Chappel[39] also considered it too drastic to decrease the daily dose of methadone by 50% when the level of 20 mg. is reached. He reported a 20 to 25% daily reduction as clinically useful.

Private methadone treatment

The American Medical Association Council report[9,11] considered methadone maintenance in the private physician's office practice not feasible because of lack of various allied therapeutic services needed for the patients, and urged physicians in private prac-

tice to cooperate with methadone maintenance programs in their communities. The Canadian Medical Association Committee report[12] took an essentially similar position. Zaks and Feldman[40] have reported a one-year experience of methadone maintenance treatment by private practitioners with favourable results. Rigg and Brawley[16] and Dole[6] have also urged the inclusion of private practitioners in methadone maintenance treatment programs because of evidence of safety and effectiveness of such treatment in private practice and because of the need for much greater availability of such treatment in the face of current prevalence of large-scale opiate dependence.

Patient selection

Selection of patients for methadone maintenance treatment usually specifically excludes those whose opiate drug-dependence is of short duration (less than two to three years) or of minimal intensity,[11,28] and would exclude persons under 18 years of age. Rosenberg and Patch[41] have reported improvement in social interaction for the majority of 52 adolescent (aged 18 to 20) patients on methadone maintenance treatment in Boston for an average of 42 weeks (with a six-month follow-up study), but also difficulty with a sizable minority who still used illicit drugs in spite of the methadone maintenance. Rigg and Brawley[16] have reported that, in Boyd's program in London (England), of 87 adolescent addicts accepted for methadone treatment, 48 were still attending after 18 months, including 8 completely off drugs, 33 maintained on low-dose methadone, and 5 maintained on high-dose methadone.

For a pregnant woman with opiate dependence, the usual recommendation[10] is to have her undergo withdrawal treatment before delivery or, if there is insufficient time to accomplish withdrawal, to maintain her on methadone through confinement and delivery, then institute withdrawal treatment after delivery. In the latter case, the infant may require treatment for withdrawal.

Methadone overdose

(−)-methadone is approximately twice as active (mg. for mg.) as morphine in its analgesic action.[18,22-23] In equianalgesic doses, methadone and morphine would produce a similar degree of respiratory depression.[25] Therefore the accidental or illicit administration of methadone in maintenance treatment doses to nontolerant or partially tolerant individuals (which could occur with improper or inadequate initial diagnosis and urinalysis evaluation of tolerance) may lead to a potentially dangerous or lethal overdose. Accidental methadone poisoning in children would be particularly serious.[42-44]

The narcotic antagonist nalorphine is usually used to counteract methadone overdose. Nalorphine possesses both agonist and antagonist properties, and therefore, in the absence of opiates, nalorphine (and also levallorphan, another commonly used narcotic antagonist) will produce its own respiratory depressant effects. Overdose of nalorphine (which could result from misjudgement of the degree of methadone or opiate overdose in the patient) would contribute to respiratory failure. It has been suggested that naloxone, which is considered to be a "pure antagonist" with no agonist properties, should be a safer agent to use for counteracting methadone overdose in emergency situations.[43,45]

In the documented experience of those who have been conducting methadone maintenance treatment programs over the past eight years,[2,8] methadone so used within such programs has been shown to be medically safe, with minimal side effects and little evidence of toxicity. Among the most common side effects are increased perspiration and constipation especially in the first 6 to 12 months of maintenance treatment, and these effects may need to be controlled by appropriate medication. Insomnia and abnormalities of sexual function (decreased libido) have also been reported by some patients.[8]

Metabolism and structure-activity relationship

Inturrisi and Verebely[46] found that methadone appeared in measurable amounts in the plasma of normal, healthy subjects 30 minutes after a 15 mg. oral dose, and reached a peak plasma level of about 0.075 μg./ml. in four hours. The plasma level then declined slowly to 40% of the peak level at 24 hours after administration, with a mean apparent half-life of 15 hours. At 96 hours after administration, an average of 52% (range 39 to 64%) of the oral dose could be accounted for, from urinary excretion, as methadone and metabolites 1 and 2. But even at 96 hours the curve describing the rate of methadone excretion had not begun to level off to a plateau. They also found that the time-action of the methadone-induced miosis closely coincided with the time-course of the methadone plasma level. In contrast, methadone's peak level in normal subjects following intramuscular administration occurred in one hour (and so did the peak miotic response). It may be noted that even at peak plasma level, the concentration of methadone in other tissues (liver, kidney, etc.) greatly exceeded the amount in the blood. Urinary excretion rate of methadone is increased under conditions of acidic urine.[47,48] *In vitro*, in human plasma albumin solution in buffer, the percentage of methadone bound to albumin has been found to be relatively independent of the concentration of methadone, but dependent on the concentration of albumin.[49]

In the human body, methadone is metabolized to "metabolite 1" (VI)[50,51] and "metabolite 2" (VII),[46,51] α-N-demethylmethadol (Vb)[48] and other metabolites (Fig. 2). Studies on animals have shown that methadone is first metabolized to methadol (Va) which is then converted to N-demethylmethadol.[48] The fact that α-N-demethylmethadol and methadol as well as the 6-amino derivative[52] (a metabolic product) of acetylmethadol are all pharmacologically active (on the basis of analgesic activity tests on animals)[48,52,53] may have some significant clinical implications. These active metabolites, together with high concentrations of methadone in tissues other than blood, and the slow excretion of orally administered methadone and acetylmethadol may partly explain the long duration of their effects in maintenance treatment and should also be taken into account in methadone overdose. Furthermore, when (±)-methadone (dl-methadone) is administered to a patient, metabolism of the relatively inactive (+)-isomer component (which is less than one tenth as active as the (−)-methadone)[18,21] yields the more active α(−)-methadol[48] (which is about one fourth as active as (−)-methadone).[53]

Government response

Before mid-1972 methadone in the long-term maintenance treatment of heroin-dependent persons was not approved for general use, but was on an investigational-drug status both in the United States and in Canada. In April 1972 the U.S. Food and Drug Administration announced its intention to remove the investigational-status designation and to make it more readily available for approved methadone maintenance programs for the treatment of heroin dependence, restricting its use to approved centres and specially authorized physicians,[7,13] but without prohibiting its use for severe pain or for acute detoxification of opiate addicts in hospital. New regulations announced by FDA in December 1972 would make methadone unavailable to ordinary physicians who have not had prior authorization to conduct such treatment programs. Procedures for applying for such authorization

were also announced. In Canada, similar new restrictions and authorization requirements came into effect on May 31, 1972, so that no physician may prescribe, administer or furnish methadone to any person unless that physician has been named in an authorization (for using methadone in a maintenance treatment program) issued by the Minister of National Health and Welfare.

Conclusion

If "success" in methadone maintenance treatment programs for heroin-dependent patients is taken to mean "having people abusing no drugs", as some critics of methadone maintenance seem to suggest that it should, then one report[17] gave methadone maintenance treatment a success rate of 2%. If "success" is measured by the rehabilitation of former heroin addicts to a "socially productive" state (i.e. employed, in school, or taking care of home), then one New York program over a six-year period is reported to have produced an 82% success-rate.[6,17] Similar success rates (similarly defined) were also reported for certain programs in California.[28] After one year's (1970-71) experience with a private methadone maintenance program in New York, Zaks and Feldman reported that 88% of the patients were employed and 82% had remained in treatment,[40] although methadone maintenance in the private physician's office practice is considered not feasible by the American Medical Association Council report,[9] and is viewed with caution in the Canadian Medical Association report.[12] The question of the definition of "success" of treatment and rehabilitation of heroin-dependent persons and the related question of whether it is right to eliminate a person's dependence on one drug by substituting dependence on another drug for long periods (years) appear to be the principal issues of controversy.[15,17] Certain other problems that have led to criticism of methadone maintenance programs are related to problems of administration of large-scale programs and control of methadone supply and diversion,[6,16,54] both of which will undoubtedly require some time for effective solution, since the rapid expansion of methadone maintenance treatment programs and new regulations for use and supply of methadone for such treatment are very recent developments. What percentage of methadone maintenance patients from large-scale programs will be successfully and completely withdrawn from methadone, and after how long a period of maintenance, will also likely require some time for a definitive assessment, although successful complete withdrawal has been reported.[55] Authoritative and medical opinions, apart from the two official association reports cited above,[9-12] have included such expressions as "uniformly favorable",[5] "persistently and startlingly good",[28] and "the cheapest and most effective weapon we have for dealing with large-scale heroin dependence."[2]

In the meantime, other modalities of medical treatment of heroin dependence have also been under study, and certain opiate antagonists with relatively longer duration of action have been reported to show some promising preliminary results.[56,57] Opiate antagonists generally have little or no addicting properties, which would be a considerable advantage if they were to prove useful in the treatment of opiate dependence. At present there are insufficient published data for drawing any definitive conclusion in that regard.

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